Remarks

Applicant thanks Examiner Solola, his supervisor Examiner McKane, and the other participating Examiners for their careful consideration of this case, and for the telephonic interview conducted on September 11, 2003. As discussed in that interview, Applicant has amended the composition and method claims in this case to recite a dosing range, and sometimes a dosing schedule, established as safe and effective in the experiments described in the present application. Applicant has also amended the composition claims to specify that the pharmaceutical carrier is selected from the group consisting of glycols, oils, and alcohols. These Amendments should not be taken as a disclaimer of any subject matter; Applicant explicitly reserves the right to pursue subject matter that was pending prior to this Amendment in other applications.

Support for Claim Amendments

As discussed in the interview, the present specification describes a variety of studies in which compositions comprising epothilone B were administered to mice in order to study both its toxicity and its efficacy. The *lowest* dose at which severe toxicity was observed was 0.6 mg/kg (see, for example, Figure 47 and Table 11 [all mice receiving 0.6 mg/kg died], as well as Figure 44B and Table 12 [5/8 mice receiving 0.8 mg/kg died, but only 1/8 mouse receiving 0.4 mg/kg died]); this dose is recited as the upper maximum in the present claims.

The data presented in the specification also demonstrate successful inhibition of tumors with regimens in which individual doses are interrupted by at least one (see, for example, Table 13; recited in claim 162) or three (see, for example, Table 8; recited in claim 163) days of rest; introducing such interruptions into the administration schedule reduced the average daily dose in almost every case to below 0.6 mg/kg, as is recited in the present claims (for example claim 150 and 158).

The data presented in the specification also demonstrate successful inhibition of multidrug-resistant tumors (see, for example, Table 8; recited in claim recited in claim 165), and show at

The present specification also describes compositions formulated for a variety of different delivery routes including parenteral (recited in claim 167) and oral (recited in claim 168) (see, for example, page 34). The specification specifically mentions glycols, oils, and alcohols are desirable pharmaceutical components (see, for example, page 34 line 16).

Thus, the present claims, as amended, are fully supported by the specification as filed. No new matter is added to the case by the present Amendments.

Nonobviousness over Bollag et al

As noted above, the Office Action rejected all pending claims as obvious in light of Bollag et al. The Office Action states that "Bollag et al., teach . . . [epothilone] B . . . and methods of use for treating cancer or tumor . . . " (page 2), and further states that "claiming variable effective amounts of the epothilones . . . is not in and of itself patentable over the prior art of Bollag et al.". Applicant strongly disagrees.

First, Applicant points out that Bollag et al. do not teach methods of using epothilone B to treat *cancer* or *a tumor*, as stated by the Examiner. Bollag et al, teach the use of a compound purified from *Sorangium cellulosum* to kill isolated cells *in vitro*. Bollag et al. do not rigorously demonstrate that the compound they isolated is epothilone B, they merely report that their spectral analyses "suggest" that their compound is the same as epothilone B described by someone else (see page 2327). *Sorangium cellulosum* are known to produce a variety of epothilone compounds and isomers; it is conceivable that the compound that Bollag et al. tested was not epothilone B at all.

Even if the compound that Bollag et al. tested was epothilone B, Bollag et al., provide no teaching or suggestion that the compound can *treat cancer* or *kill tumors*. The mere demonstration that a compound can kill cells *in vitro* cannot render obvious the present claims to compositions reciting particular amounts of that compound that are effective at treating cancer or

invitation to experiment, to *try to identify* an amount of the compound that could be useful in treating cancer or inhibiting tumor growth. There was no reasonable expectation, based merely on the teachings of Bollag et al., that such an amount could be identified.

In fact, as Applicant has previously indicated and has been discussed in both in-person and telephonic interviews, epothilone B shows unexpectedly severe toxicity. The data presented in the present specification attest to the challenges associated with defining a therapeutic index for epothilone B. The present specification establishes that doses above 0.6 mg/kg often result in unacceptable toxicity (see, for example, Figure 47 and Table 11; see also Figure 44B and Table 12). In one experiment, *all* mice receiving this dose died!

For all of these reasons, Applicant respectfully submits that the teachings of Bollag et al. cannot render obvious the present claims; the rejection can be removed.

Double Patenting

In the Office Action, all claims were provisionally rejected for statutory double patenting over claims 59-95 of USSN 10/058,695. Applicant respectfully refrains from commenting on this rejection unless and until such time as it matures into an actual rejection.

Objection to Claims

In the Office Action, the Examiner objected to claims 144-149 as substantial duplicates. The present Amendments cancel claims 145, 146 and 149, and amend claims 144, 147, and 148. Applicant submits that these Amendments obviate the objection.

Conclusion

In light of the foregoing Amendments and Remarks, Applicant respectfully submits that the present application is in condition for allowance; a Notice to that effect is respectfully requested.

If it is believed that a telephone conversation would expedite matters, the Examiner is invited to

The Examiner is authorized to charge any fees associated with this amendment, or to refund for any overpayment, to our Deposit Account No.: 03-1721.

Respectfully submitted,

Brenda Herschbach Jarrell, Ph.D.
Registration Number 39,223

PATENT DEPARTMENT
CHOATE, HALL & STEWART
Exchange Place
53 State Street
Boston, MA 02109
Attn: Brenda Herschbach Jarrell, Ph.D.
(617) 248-5000

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